

What Is Claimed Is:

1. An ApoA-I agonist comprising:

(i) a 15 to 29-residue peptide or peptide analogue which  
5 forms an amphipathic  $\alpha$ -helix in the presence of lipids and  
which comprises the structural formula (I):

$Z_1-X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}-X_{14}-X_{15}-X_{16}-X_{17}-X_{18}-X_{19}-X_{20}-X_{21}-X_{22}-X_{23}-Z_2$

10 or a pharmaceutically acceptable salt thereof, wherein:

$X_1$  is Pro (P), Ala (A), Gly (G), Gln (Q), Asn (N),  
Asp (D) or D-Pro (p);

$X_2$  is an aliphatic residue;

$X_3$  is Leu (L) or Phe (F);

15  $X_4$  is an acidic residue;

$X_5$  is Leu (L) or Phe (F);

$X_6$  is Leu (L) or Phe (F);

$X_7$  is a hydrophilic residue;

$X_8$  is an acidic or a basic residue;

20  $X_9$  is Leu (L) or Gly (G);

$X_{10}$  is Leu (L), Trp (W) or Gly (G);

$X_{11}$  is a hydrophilic residue;

$X_{12}$  is a hydrophilic residue;

$X_{13}$  is Gly (G) or an aliphatic residue;

25  $X_{14}$  is Leu (L), Trp (W), Gly (G) or Nal;

$X_{15}$  is a hydrophilic residue;

$X_{16}$  is a hydrophobic residue;

$X_{17}$  is a hydrophobic residue;

$X_{18}$  is Gln (Q), Asn (N) or a basic residue;

30  $X_{19}$  is Gln (Q), Asn (N) or a basic residue;

$X_{20}$  is a basic residue;

$X_{21}$  is an aliphatic residue;

$X_{22}$  is a basic residue;

$X_{23}$  is absent or a basic residue;

35  $Z_1$  is  $H_2N-$  or  $RC(O)NH-$ ;

$Z_2$  is  $-C(O)NRR$ ,  $-C(O)OR$  or  $-C(O)OH$  or a salt thereof;

each R is independently  $-H$ ,  $(C_1-C_6)$  alkyl,  $(C_1-C_6)$  alkenyl,  $(C_1-C_6)$  alkynyl,  $(C_5-C_{20})$  aryl,  $(C_6-C_{26})$  alkaryl, 5-20 membered heteroaryl, 6-26 membered alkheteroaryl or a 1 to 7-residue peptide or peptide analogue;

each " - " between residues  $X_n$  independently designates an amide linkage, a substituted amide linkage, an isostere of an amide or an amide mimetic; or

(ii) a deleted from of structural formula (I) in which at least one and up to eight of residues  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ ,  $X_5$ ,  $X_6$ ,  $X_7$ ,  $X_8$ ,  $X_9$ ,  $X_{10}$ ,  $X_{11}$ ,  $X_{12}$ ,  $X_{13}$ ,  $X_{14}$ ,  $X_{15}$ ,  $X_{16}$ ,  $X_{17}$ ,  $X_{18}$ ,  $X_{19}$ ,  $X_{20}$ ,  $X_{21}$  and  $X_{22}$  are deleted; or

(iii) an altered form of structural formula (I) in which at least one of residues  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ ,  $X_5$ ,  $X_6$ ,  $X_7$ ,  $X_8$ ,  $X_9$ ,  $X_{10}$ ,  $X_{11}$ ,  $X_{12}$ ,  $X_{13}$ ,  $X_{14}$ ,  $X_{15}$ ,  $X_{16}$ ,  $X_{17}$ ,  $X_{18}$ ,  $X_{19}$ ,  $X_{20}$ ,  $X_{21}$ ,  $X_{22}$  or  $X_{23}$  is conservatively substituted with another residue.

2. The ApoA-I agonist of Claim 1 which exhibits at least about 38% LCAT-activation activity as compared with human ApoA-I.

3. The ApoA-I agonist of Claim 1 which is the altered form of structural formula (I).

4. The ApoA-I agonist of Claim 3 in which the hydrophobic residues are fixed according to structural formula (I) and at least one non-fixed residue is conservatively substituted with another residue.

5. The ApoA-I agonist of Claim 4 in which:

$X_1$  is Pro (P), D-Pro (p), Gly (G) or Ala (A);

$X_2$  is Ala (A), Leu (L) or Val (V);

$X_3$  is Leu (L) or Phe (F);

X<sub>5</sub> is Leu (L) or Phe (F);  
X<sub>6</sub> is Leu (L) or Phe (F);  
X<sub>9</sub> is Leu (L) or Gly (G);  
X<sub>10</sub> is Leu (L), Trp (W) or Gly (G);  
5 X<sub>13</sub> is Leu (L), Gly (G) or Aib;  
X<sub>14</sub> is Leu, Nal, Trp (W) or Gly (G);  
X<sub>16</sub> is Ala (A), Nal, Trp (W), Gly (G), Leu (L) or  
Phe (F);  
X<sub>17</sub> is Leu (L), Gly (G) or Nal;  
10 X<sub>21</sub> is Leu (L); and

at least one of X<sub>4</sub>, X<sub>7</sub>, X<sub>8</sub>, X<sub>11</sub>, X<sub>12</sub>, X<sub>15</sub>, X<sub>18</sub>, X<sub>19</sub>, X<sub>20</sub>, X<sub>22</sub>  
and X<sub>23</sub> is conservatively substituted with another residue.

6. The ApoA-I agonist of Claim 3 in which the  
15 hydrophilic residues are fixed according to structural  
formula (I) and at least one non-fixed residue is  
conservatively substituted with another residue.

7. The ApoA-I agonist of Claim 6 in which:  
20 X<sub>4</sub> is Asp (D) or Glu (E);  
X<sub>7</sub> is Lys (K), Arg (R) or Orn;  
X<sub>8</sub> is Asp (D) or Glu (E);  
X<sub>11</sub> is Asn (N) or Gln (Q);  
X<sub>12</sub> is Glu (E) or Asp (D);  
25 X<sub>15</sub> is Asp (D) or Glu (E);  
X<sub>18</sub> is Gln (Q), Asn (N), Lys (K) or Orn;  
X<sub>19</sub> is Gln (Q), Asn (N), Lys (K) or Orn;  
X<sub>20</sub> is Lys (K) or Orn;  
X<sub>22</sub> is Lys (K) or Orn;  
30 X<sub>23</sub> is absent or Lys (K); and  
at least one of X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>5</sub>, X<sub>6</sub>, X<sub>9</sub>, X<sub>10</sub>, X<sub>13</sub>, X<sub>14</sub>, X<sub>16</sub>, X<sub>17</sub>  
and X<sub>21</sub> is conservatively substituted with another residue.

8. The ApoA-I agonist of Claim 7 in which X<sub>3</sub> is Leu (L)  
35 or Phe (F), X<sub>6</sub> is Phe (F), X<sub>9</sub> is Leu (L) or Gly (G), X<sub>10</sub> is Leu  
(L) or Trp (W) or Gly (G) and at least one of X<sub>4</sub>, X<sub>2</sub>, X<sub>5</sub>, X<sub>13</sub>,

X<sub>14</sub>, X<sub>16</sub>, X<sub>17</sub> and X<sub>21</sub> is conservatively substituted with another residue.

5           9.    The ApoA-I agonist of Claim 5 or 7 in which the substituting residue is classified within the same sub-category as the substituted residue.

10           10.   The ApoA-I agonist of Claim 1 which is the deleted form of structural formula (I).

          11.    The ApoA-I agonist of Claim 10 in which one helical turn of the peptide or peptide analogue is deleted.

15           12.    The ApoA-I agonist of Claim 1 which is a 22-23 residue peptide or peptide analogue of structural formula (I).

20           13.    The ApoA-I agonist of Claim 12 in which:  
                the "-" between residues designates -C(O)NH-;  
                Z<sub>1</sub> is H<sub>2</sub>N-; and  
                Z<sub>2</sub> is -C(O)OH or a salt thereof.

25           14.    The ApoA-I agonist of Claim 13, in which:  
                X<sub>1</sub> is Pro (P), Ala (A), Gly (G), Asn (N), Gln (Q),  
                Asp (D) or D-Pro (p);  
                X<sub>2</sub> is Ala (A), Val (V) or Leu (L);  
                X<sub>3</sub> is Leu (L) or Phe (F);  
                X<sub>4</sub> is Asp (D) or Glu (E);  
                X<sub>5</sub> is Leu (L) or Phe (F);  
30               X<sub>6</sub> is Leu (L) or Phe (F);  
                X<sub>7</sub> is Lys (K), Arg (R) or Orn;  
                X<sub>8</sub> is Asp (D) or Glu (E);  
                X<sub>9</sub> is Leu (L) or Gly (G);  
                X<sub>10</sub> is Leu (L), Trp (W) or Gly (G);  
35               X<sub>11</sub> is Asn (N) or Gln (Q);  
                X<sub>12</sub> is Glu (E) or Asp (D);

X<sub>13</sub> is Gly (G), Leu (L) or Aib;  
 X<sub>14</sub> is Leu (L), Nal, Trp (W) or Gly (G);  
 X<sub>15</sub> is Asp (D) or Glu (E);  
 X<sub>16</sub> is Ala (A), Nal, Trp (W), Leu (L), Phe (F) or  
 Gly (G);  
 X<sub>17</sub> is Gly (G), Leu (L) or Nal;  
 X<sub>18</sub> is Gln (Q), Asn (N), Lys (K) or Orn;  
 X<sub>19</sub> is Gln (Q), Asn (N), Lys (K) or Orn;  
 X<sub>20</sub> is Lys (K) or Orn;  
 X<sub>21</sub> is Leu (L);  
 X<sub>22</sub> is Lys (K) or Orn; and  
 X<sub>23</sub> is absent or Lys (K).

15. The ApoA-I agonist of Claim 14, in which X<sub>23</sub> is  
 absent.

16. The ApoA-I agonist of Claim 13 or 14, in which one  
 of X<sub>18</sub> or X<sub>19</sub> is Gln (Q) or Asn (N) and the other of X<sub>18</sub> or X<sub>19</sub>  
 is Lys (K) or Orn.

17. The ApoA-I agonist of Claim 14 in which each of X<sub>9</sub>,  
 X<sub>10</sub>, X<sub>13</sub>, X<sub>14</sub>, X<sub>15</sub> and X<sub>17</sub> is other than Gly (G).

18. The ApoA-I agonist of Claim 14 in which one of X<sub>9</sub>,  
 X<sub>10</sub>, X<sub>13</sub>, X<sub>14</sub>, X<sub>15</sub> and X<sub>17</sub> is Gly (G) and the others are other  
 than Gly (G).

19. The ApoA-I agonist of Claim 1 which is selected  
 from the group consisting of:

peptide 1	PVLDLFRELLNELLEZLKQKLK	(SEQ ID NO:1)
peptide 2	GVLDLFRELLNELLEALKQKLKK	(SEQ ID NO:2)
peptide 3	PVLDLFRELLNELLEWLKQKLK	(SEQ ID NO:3)
peptide 4	PVLDLFRELLNELLEALKQKLK	(SEQ ID NO:4)
peptide 5	pVLDLFRELLNELLEALKQKLKK	(SEQ ID NO:5)
peptide 6	PVLDLFRELLNEXLEALKQKLK	(SEQ ID NO:6)

	peptide 7	PVLDLDFKELLNELLEALKQKCLK	(SEQ ID NO:7)
	peptide 8	PVLDLDFRELLNEGLEALKQKCLK	(SEQ ID NO:8)
	peptide 9	PVLDLDFRELGNELLEALKQKCLK	(SEQ ID NO:9)
	peptide 10	PVLDLDFRELLNELLEAZKQKCLK	(SEQ ID NO:10)
5	peptide 11	PVLDLDFKELLQELLEALKQKCLK	(SEQ ID NO:11)
	peptide 12	PVLDLDFRELLNELLEAGKQKCLK	(SEQ ID NO:12)
	peptide 13	GVLDLDFRELLNEGLEALKQKCLK	(SEQ ID NO:13)
	peptide 14	PVLDLDFRELLNELLEALOQOLO	(SEQ ID NO:14)
	peptide 15	PVLDLDFRELWNELLEALKQKCLK	(SEQ ID NO:15)
10	peptide 16	PVLDLLRELLNELLEALKQKCLK	(SEQ ID NO:16)
	peptide 17	PVLELFKELLQELLEALKQKCLK	(SEQ ID NO:17)
	peptide 18	GVLDLDFRELLNELLEALKQKCLK	(SEQ ID NO:18)
	peptide 19	pVLDLDFRELLNEGLEALKQKCLK	(SEQ ID NO:19)
	peptide 20	PVLDLDFREGLNELLEALKQKCLK	(SEQ ID NO:20)
15	peptide 21	pVLDLDFRELLNELLEALKQKCLK	(SEQ ID NO:21)
	peptide 22	PVLDLDFRELLNELLEGLKQKCLK	(SEQ ID NO:22)
	peptide 23	PLLELFKELLQELLEALKQKCLK	(SEQ ID NO:23)
	peptide 24	PVLDLDFRELLNELLEALQKKCLK	(SEQ ID NO:24)
	peptide 25	PVLDLDFRELLNEXLEALKQKCLK	(SEQ ID NO:25)
20	peptide 26	PVLDLDFRELLNELLELLKQKCLK	(SEQ ID NO:26)
	peptide 27	PVLDLDFRELLNELZEALKQKCLK	(SEQ ID NO:27)
	peptide 28	PVLDLDFRELLNELWEALKQKCLK	(SEQ ID NO:28)
	peptide 29	AVLDLDFRELLNELLEALKQKCLK	(SEQ ID NO:29)
	peptide 123	QVLDLDFRELLNELLEALKQKCLK	(SEQ ID NO:123)
25	peptide 124	PVLDLDFOELLNELLEALOQOLO	(SEQ ID NO:124)
	peptide 125	NVLDLDFRELLNELLEALKQKCLK	(SEQ ID NO:125)
	peptide 126	PVLDLDFRELLNELGEALKQKCLK	(SEQ ID NO:126)
	peptide 127	PVLDLDFRELLNELLELLKQKCLK	(SEQ ID NO:127)
	peptide 128	PVLDLDFRELLNELLEFLKQKCLK	(SEQ ID NO:128)
30	peptide 129	PVLELFNDLLRELLEALQKKCLK	(SEQ ID NO:129)
	peptide 130	PVLELFNDLLRELLEALKQKCLK	(SEQ ID NO:130)
	peptide 131	PVLELFKELLNELLDALRQKCLK	(SEQ ID NO:131)
	peptide 132	PVLDLDFRELLNLEALQKKCLK	(SEQ ID NO:132)

peptide 133 PVLELFFERLLEDLLQALNKKLK (SEQ ID NO:133)  
 peptide 134 PVLELFFERLLEDLLKALNQKLK (SEQ ID NO:134)  
 peptide 135 DVLDLFFRELLNELLEALKQKLK (SEQ ID NO:135)  
 peptide 136 PALELFFKDLLQELLEALKQKLK (SEQ ID NO:136)  
 5 peptide 137 PVLDLFFRELLNEGLEAZKQKLK (SEQ ID NO:137)  
 peptide 138 PVLDLFFRELLNEGLEWLKQKLK (SEQ ID NO:138)  
 peptide 139 PVLDLFFRELWNEGLEALKQKLK (SEQ ID NO:139)  
 peptide 140 PVLDLFFRELLNEGLEALOOLO (SEQ ID NO:140)  
 peptide 141 PVLDLFFRELLNEGLEALKQKLK (SEQ ID NO:141)  
 10 peptide 142 PVLELFFRELLNEGLEALKQKLK (SEQ ID NO:142)

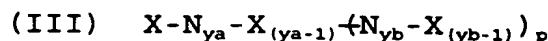
and the N-terminal acylated and/or C-terminal amidated or esterified forms thereof, wherein X is Aib; Z is Nal; and O is Orn.

20. A multimeric ApoA-I agonist which exhibits at least about 38% LCAT activation activity as compared with human ApoA-I and which has the structural formula (II):



or a pharmaceutically acceptable salt thereof, wherein:  
 each m is independently an integer from 0 to 1;  
 n is an integer from 0 to 10;  
 25 each "HH" is independently a peptide or peptide analogue according to Claim 1;  
 each "LL" is independently a bifunctional linker;  
 and  
 each " - " independently designates a covalent  
 30 linkage.

21. A multimeric ApoA-I agonist which exhibits at least about 38% LCAT activation activity as compared with human ApoA-I and which has the structural formula (III):



or a pharmaceutically acceptable salt thereof, wherein:

each X is independently  $\text{HH}(\text{LL}_m\text{--HH})_n\text{LL}_m\text{--HH}$ ;

each HH is independently a core peptide of structure (I) or an analogue or mutated, truncated, internally deleted or extended form thereof as described herein;

each LL is independently a bifunctional linker;

each m is independently an integer from 0 to 1;

each n is independently an integer from 0 to 8;

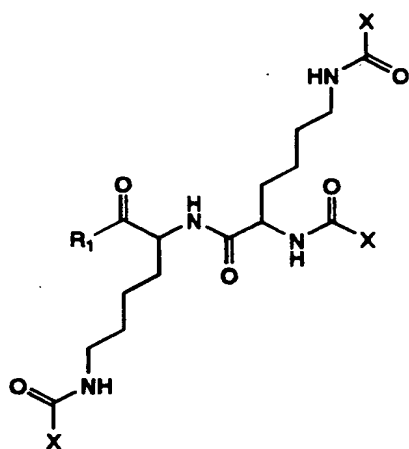
$N_{ya}$  and  $N_{yb}$  are each independently a multifunctional linking moiety where  $y_a$  and  $y_b$  represent the number of functional groups on  $N_{ya}$  and  $N_{yb}$ , respectively;

each  $y_a$  or  $y_b$  is independently an integer from 3 to 8;

p is an integer from 0 to 7; and

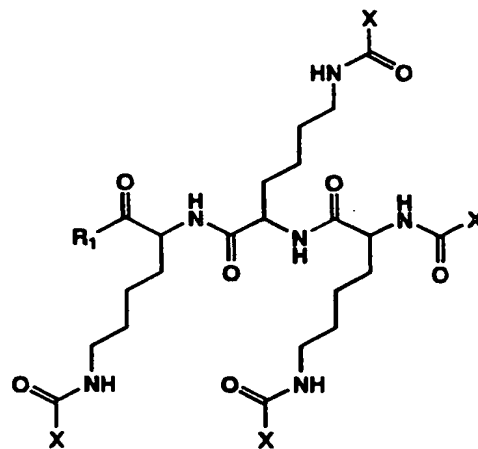
each "--" independently designates a covalent bond.

22. A multimeric ApoA-I agonist which exhibits at least about 38% LCAT activation activity as compared with human ApoA-I and which has the structural formula (IV) or (V):



(IV)

-OR-



(V)

or a pharmaceutically acceptable salt thereof, wherein:



each X is independently  $\text{HH}(\text{LL}_m\text{-HH})_n\text{LL}_m\text{-HH}$ ;  
each HH is independently a peptide or peptide  
analogue according to Claim 1;  
each LL is independently a bifunctional linker;  
5 each n is independently an integer from 0 to 1;  
each m is independently an integer from 0 to 8;  
 $R_1$  is -OR or -NRR; and  
each R is independently -H,  $(C_1-C_6)$  alkyl,  $(C_1-C_6)$   
alkenyl,  $(C_1-C_6)$  alkynyl;  $(C_5-C_{20})$  aryl  $(C_6-C_{26})$  alkaryl, 5-20  
10 membered heteroaryl or 6-26 membered alkheteroaryl.

23. The multimeric ApoA-I agonist of Claim 20, 21 or 22  
in which the bifunctional linker is cleavable.

15 24. The ApoA-I multimeric agonist of Claim 20, 21 or 22  
in which n is 0.

25 25. The multimeric ApoA-I agonist of Claim 24 in which  
m is 0.

20 26. The multimeric ApoA-I agonist of Claim 20, 21 or 22  
in which each HH is independently a peptide according to  
Claim 13.

25 27. The multimeric ApoA-I agonist of Claim 20, 21 or 22  
in which each HH is independently a peptide according to  
Claim 14.

30 28. The multimeric ApoA-I agonist of Claim 20, 21 or 22  
in which each HH is independently a peptide according to  
Claim 19.

35 29. An ApoA-I agonist-lipid complex comprising an  
ApoA-I agonist and a lipid, wherein the ApoA-I agonist is a  
peptide or peptide analogue according to Claim 1, a  
multimeric ApoA-I agonist according to Claim 20, a multimeric

ApoA-I agonist according to Claim 21, or a multimeric ApoA-I agonist according to Claim 22.

5           30. The ApoA-I agonist-lipid complex of Claim 29 in which the ApoA-I agonist is a peptide according to Claim 12.

          31. The ApoA-I agonist-lipid complex of Claim 29 in which the ApoA-I agonist is a peptide according to Claim 13.

10           32. The ApoA-I agonist-lipid complex of Claim 29 in which the ApoA-I agonist is a peptide according to Claim 14.

          33. The ApoA-I agonist-lipid complex of Claim 29 in which the ApoA-I agonist is a peptide according to Claim 19.

15           34. The ApoA-I agonist-lipid complex of Claim 29 in which the lipid is sphingomyelin.

          35. The ApoA-I agonist-lipid complex of Claim 29 which is in the form of a lyophilized powder.

20           36. The ApoA-I agonist-lipid complex of Claim 29 which is in the form of a solution.

25           37. A pharmaceutical composition comprising an ApoA-I agonist and a pharmaceutically acceptable carrier, excipient or diluent, wherein the ApoA-I agonist is a peptide or peptide analogue according to Claim 1, a multimeric ApoA-I agonist according to Claim 20, a multimeric ApoA-I agonist according to Claim 21, or a multimeric ApoA-I agonist according to Claim 22.

30           38. The pharmaceutical composition of Claim 37 in which the ApoA-I agonist is a peptide according to Claim 12.

39. The pharmaceutical composition of Claim 37 in which the ApoA-I agonist is a peptide according to Claim 13.

5 40. The pharmaceutical composition of Claim 37 in which the ApoA-I agonist is a peptide according to Claim 14.

41. The pharmaceutical composition of Claim 37 in which the ApoA-I agonist is a peptide according to Claim 19.

10 42. The pharmaceutical composition of Claim 37, 38, 39, 40 or 41, in which the ApoA-I agonist is in the form of an ApoA-I agonist-lipid complex, said complex comprising the ApoA-I agonist and a lipid.

15 43. The pharmaceutical composition of Claim 42 in which the ApoA-I agonist-lipid complex is in the form of a lyophilized powder.

20 44. A method of treating a subject suffering from a disorder associated with dyslipidemia, said method comprising the step of administering to the subject an effective amount of the ApoA-I agonist of Claim 1.

25 45. The method of Claim 44 in which the ApoA-I agonist is in the form of a pharmaceutical composition, said composition comprising the ApoA-I agonist and a pharmaceutically acceptable carrier, excipient or diluent.

30 46. The method of Claim 44 in which the ApoA-I agonist is in the form of an ApoA-I agonist-lipid complex, said complex comprising the ApoA-I agonist and a lipid.

35 47. The method of Claim 44 in which the disorder associated with dyslipidemia is hypercholesterolemia.

48. The method of Claim 44 in which the disorder associated with dyslipidemia is cardiovascular disease.

5 49. The method of Claim 44 in which the disorder associated with dyslipidemia is atherosclerosis.

50. The method of Claim 44 in which the disorder associated with dyslipidemia is restenosis.

10 51. The method of Claim 44, in which the disorder associated with dyslipidemia is HDL or ApoA-I deficiency.

15 52. The method of Claim 44, in which the disorder associated with dyslipidemia is hypertriglyceridemia.

53. The method of Claim 44, in which the disorder associated with dyslipidemia is metabolic syndrome.

20 54. A method of treating a subject suffering from septic shock, said method comprising the step of administering to the subject an effective amount of the ApoA-I agonist of Claim 1.

25 55. The method of Claim 44 or 54 in which said subject is a human.

56. The method of Claim 44 or 54 in which about 0.5 mg/kg to about 100 mg/kg ApoA-I agonist is administered to said subject.